



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/02, 47/26	A1	(11) International Publication Number: WO 95/33487 (43) International Publication Date: 14 December 1995 (14.12.95)
(21) International Application Number: PCT/EP95/02127 (22) International Filing Date: 2 June 1995 (02.06.95) (30) Priority Data: MI94A001169 6 June 1994 (06.06.94) IT (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM FARMACEUTICI S.P.A. [IT/IT]; Via Zambeletti, I-20021 Baranzate (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): FONIO, Teodoro [IT/IT]; SmithKline Beecham Farmaceutici S.p.A., Via Zambeletti, I-20021 Baranzate (IT). PESATORI, Marco [IT/IT]; SmithKline Beecham Farmaceutici S.p.A., Via Zambeletti, I-20021 Baranzate (IT). (74) Agent: WALKER, Ralph, Francis; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INJECTABLE FORMULATIONS CONTAINING A DESICCANT (57) Abstract A pharmaceutical formulation comprising a moisture sensitive pharmaceutically active material and a desiccant material, the desiccant being both water soluble and pharmaceutically acceptable by parenteral administration. The formulation is suitable for parenteral administration.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Injectable formulations containing a desiccant

This invention relates to pharmaceutical formulations suitable for parenteral administration.

5 Pharmaceutical formulations for parenteral administration, which term includes injection and infusion, e.g. intravenously (i.v.) or intramuscularly (i.m.), are normally available as ready to use solutions and suspensions provided in sealed vials or ampoules, or as solid formulations, e.g. granules and powders, provided in sealed vials ready for reconstitution with an aqueous medium such as sterile water.

10 Problems can occur on long term storage of such solid formulations, for example in the vials in which they are supplied or in containers in which they are stored, when components of the formulation are significantly moisture sensitive, e.g. hygroscopic and/or readily hydrolysable, as containers can allow slow ingress of atmospheric moisture, and moreover there may be traces of water in the air and/or
15 in one or more components of the formulation and/or in the container before it is sealed.

One type of such moisture sensitive formulations are those which include pharmaceutically acceptable derivatives of the β -lactamase inhibitor clavulanic acid (hereinafter referred to as "clavulanate" unless specific derivatives are identified),
20 such as its salts, particularly potassium clavulanate, which is very moisture sensitive. Potassium clavulanate is frequently co-formulated with β -lactam antibiotics in injectable formulations, such as with injectable forms of amoxycillin, for example sodium amoxycillin.

In commonly used co-formulations of potassium clavulanate and sodium
25 amoxycillin, an amorphous spray dried form of sodium amoxycillin is used. Spray dried sodium amoxycillin is a powerful desiccant and when co-formulated with potassium clavulanate in a sealed vial it can serve to protect the potassium clavulanate from the effects of moisture. EP 0131147 discloses a crystalline form of sodium amoxycillin, which is of greater purity than spray-dried sodium
30 amoxycillin. It is clearly desirable to co-formulate potassium clavulanate with such a purer form of sodium amoxycillin, but when this is done the problem is encountered that the purer crystalline form of sodium amoxycillin has no or very little desiccant ability, and does not significantly protect the potassium clavulanate from degradation by moisture.

35 Tablet formulations comprising potassium clavulanate have included desiccants as part of the tablet formulation, e.g. as disclosed in GB 2084016. But clearly the desiccants used therein, silica gel and molecular sieve, are unsuitable for injectable formulations.

It is an object of this invention to provide desiccated pharmaceutical

formulations suitable for administration by injection or infusion, particularly formulations comprising potassium clavulanate and sodium amoxycillin. Other objects and advantages of the present invention will be apparent from the following description.

5 According to this invention a pharmaceutical formulation is provided, comprising a moisture sensitive pharmaceutically active material and a desiccant material, the desiccant being both water soluble and pharmaceutically acceptable by parenteral administration.

10 The present invention also provides a method of preparing such a formulation, comprising the steps of admixing a moisture sensitive pharmaceutically active material and a desiccant, the desiccant being both water soluble and pharmaceutically acceptable by injection or infusion.

 The present invention also provides such a formulation for use as an active therapeutic substance.

15 The present invention also provides the use of such a formulation in the preparation of a medicament.

 The present invention also provides a method for protecting a moisture sensitive pharmaceutically active material from degradation by moisture by the use of a desiccant material which is both water soluble and pharmaceutically acceptable by parenteral administration.

20 The present invention also provides a method of treatment of a human patient which includes the step of the parenteral administration to a patient in need of such treatment of a formulation as described above.

25 In the formulation of the invention the desiccant exercises a desiccant effect upon the moisture sensitive pharmaceutically active material and thereby protects it against the effects of moisture. Moreover by virtue of being pharmaceutically acceptable by parenteral administration the formulation may be made up into solution together with the active material for parenteral administration, for example via i.v. or i.m. administration.

30 The formulation of the invention is suitable for parenteral administration. The moisture sensitive pharmaceutically active material is preferably one which is suitable for parenteral administration. The formulation of the invention may additionally include pharmaceutically active material(s) which are stable to moisture and which are suitable for parenteral administration.

35 The invention is particularly suitable for use in formulations wherein the moisture sensitive pharmaceutically active material is clavulanate, particularly potassium clavulanate. The clavulanate may be co-formulated with an injectable antibiotic, suitably a β -lactam antibiotic, such as a penicillin or cephalosporin, so

that the formulation is suitable for use in the treatment of bacterial infections. The antibiotic may be in a crystalline form, and may also be moisture sensitive, or may be stable toward moisture.

5 Preferred β -lactam antibiotics are amoxycillin and ticarcillin in the form of respectively sodium amoxycillin and sodium ticarcillin. A particular form of sodium amoxycillin for which the present invention is suitable is crystalline sodium amoxycillin, particularly anhydrous crystalline sodium amoxycillin, for example the crystalline sodium amoxycillin disclosed in EP 0131147, the contents of which are included by way of reference.

10 In such a co-formulation of potassium clavulanate and an antibiotic such as sodium amoxycillin or sodium ticarcillin the ratio potassium clavulanate : antibiotic may vary within known broad limits, typically between 1 : 1 and 1 : 30, particularly between 1 : 1 and 1 : 12 in the case of sodium amoxycillin, for example between 1 : 1 and 1 : 8, these ratios being expressed in terms of the free acid
15 equivalents.

In such a formulation the quantities of active materials may be present in unit or multiple unit dosage amounts, corresponding to the quantities in which they are used in known injectable formulations. For example in the case of injectable potassium clavulanate : sodium amoxycillin formulations 100 mg clavulanic acid :
20 500 mg amoxycillin, or 200 mg clavulanic acid : 1000 mg amoxycillin, provided respectively as potassium clavulanate and sodium amoxycillin may be used in unit dosage or multiple unit dosage formulations.

A suitable desiccant is a desiccating metal salt which is water soluble and pharmaceutically acceptable when administered by injection. Examples of such salts
25 which have been found to be suitable, particularly for formulations which comprise clavulanate, for example co-formulations of potassium clavulanate and crystalline sodium amoxycillin, include Group I and Group II metal chlorides or mixtures thereof, such as desiccating forms of sodium chloride, calcium chloride and magnesium chloride.

30 A suitable desiccating form of sodium chloride is an amorphous form for example obtainable by spray-drying and containing a low moisture content. A suitable desiccating form of calcium chloride is an at least partly dehydrated form, e.g containing 5% or less of water, for example obtainable by heat treatment under vacuum. A suitable desiccating form of magnesium chloride is an at least partly
35 dehydrated form, for example obtainable by heat treatment under vacuum.

Other metal salts which may be suitable include disodium phosphate in an at least partly anhydrous form e.g containing around 0.1% water. Such salts may be used singly or in mixtures, for example a mixture of sodium chloride and

magnesium chloride.

The quantity of a desiccating metal salt needed to provide adequate desiccation of the pharmaceutical formulation of the invention will depend upon the components of the formulation and in particular on the nature of the moisture sensitive active material. In the case of formulations comprising potassium clavulanate, 2200 mg of a 10:1 sodium amoxycillin : potassium clavulanate blend (ratio expressed as weights of free acids equivalent) contained in a sealed vial for injectable administration may be suitably protected by 50 mg or less, e.g 35 - 15 mg of magnesium chloride, or by 200 mg or less, e.g 100 mg or less, of sodium chloride, or by 100 mg or less of a 95:5 w:w mixture of sodium chloride and magnesium chloride, or by 100 mg or less, e.g 50 mg or less of calcium chloride.

Another suitable desiccant is a desiccating carbohydrate which is water soluble and pharmaceutically acceptable when administered by injection. Examples of such desiccating carbohydrates include lactose (particularly in a spray-dried form) sorbitol, and glucose, in an at least partly dehydrated state, for example obtainable by heat treatment under vacuum. Lactose is a preferred desiccating carbohydrate. Desiccating carbohydrates may be used singly, or mixtures of desiccating carbohydrates may be used, or mixtures of one or more desiccating carbohydrates with one or more of the above-described desiccating metal salts may be used.

The quantity of a desiccating carbohydrate needed to provide adequate desiccation of the pharmaceutical formulation of the invention will again depend upon the components of the formulation and in particular on the nature of the moisture sensitive active material. In the case of formulations comprising potassium clavulanate, 2200 mg of a 10:1 sodium amoxycillin : potassium clavulanate blend (ratio expressed as weights of free acids equivalent) contained in a sealed vial for injectable administration may be suitably protected by 500 mg or less of a desiccating form of glucose, sorbitol or spray-dried lactose.

Another suitable desiccant is a desiccating form of a polyvinylpyrrolidone ("PVP") polymer, such as the polymers commercially available as Kollidon 17 PF [™] and Kollidon 12 PF [™]. The use of PVP in the form of Kollidon PF 12 [™] together only with sodium amoxycillin in injectable pharmaceutical formulations to improve the stability of the sodium amoxycillin when the formulation has been reconstituted has previously been disclosed in EP 0012495 A and EP 0012496 A. However the PVP is not functioning as a desiccant in such formulations, as EP 0012495 states that the PVP may even be provided as an aqueous solution. EP 0012495 discloses a formulation comprising 250 mg of precipitated sodium amoxycillin and 1000 mg of Kollidon PF 12 [™]. The sodium amoxycillin disclosed in EP 0012495 is an unstable

amorphous material, not the crystalline anhydrous form of sodium amoxycillin disclosed in EP 0131147, and moreover the examples of EP 0012495 include the use of spray dried sodium amoxycillin which is a desiccant per se.

5 The quantity of a desiccating form of PVP needed to provide adequate desiccation of the pharmaceutical formulation of the invention will again depend upon the components of the formulation and in particular on the nature of the moisture sensitive active material. In the case of formulations comprising potassium clavulanate, 2200 mg of a 10:1 sodium amoxycillin : potassium clavulanate blend (ratio expressed as weights of free acids equivalent) contained in a sealed vial for
10 injectable administration may be suitably protected by 500 mg or less, e.g 100 mg or less, e.g ca. 30 mg of a desiccating form of PVP.

Mixtures of two or more of the above-mentioned classes of desiccants may be used, for example of a desiccating metal salt and a desiccating carbohydrate such as spray dried lactose.

15 The weights of the above mentioned desiccants suggested above to protect the above mentioned weights of sodium amoxycillin : potassium clavulanate blend suggest by extrapolation or interpolation which will be apparent to those skilled in the art suitable weight : weight ratios for protection of other weights of potassium clavulanate by such desiccants.

20 Preferred formulations of the invention are those comprising crystalline sodium amoxycillin, potassium clavulanate and as a desiccant magnesium chloride, sodium chloride or spray-dried lactose. Of these desiccants magnesium chloride is particularly preferred.

25 The method of protecting a moisture sensitive pharmaceutically active material from degradation by moisture provided by this invention is suitable for use in the protection of formulations contained in sealed containers.

The formulation may be a formulation which on reconstitution with water yields a solution or suspension which is suitable for administration by injection. Formulations for administration by injection are normally provided in sealed vials,
30 and the present invention therefore also includes sealed vials containing such a formulation. When sealing such a formulation into vials it is advisable to take additional physical precautions to reduce the ingress of atmospheric moisture, for example the use of vials made of substantially impermeable materials such as glass, provided with efficient stoppers. If the formulation includes potassium clavulanate
35 the formulations are preferably filled in conditions of low relative humidity, typically around 30% RH or lower.

The formulations of the invention may also include the excipients which are often included in injectable formulations, for example local anaesthetics,

preservatives, buffering agents, surfactants and wetting agents etc. Such materials, and appropriate quantities in which they may be used, are known in the art, for example for use in injectable potassium clavulanate : sodium amoxycillin co-formulations. Alternatively such materials may be included in the medium with
5 which the formulations are made up.

The formulation may be sterilised in a known way for example with ethylene oxide. Alternatively individual sterile components of the formulation can be blended in a sterile area.

Formulations of the invention may be formulated in any suitable way, for
10 example by simply admixing the dried, powdered or granulated constituents, either prior to introducing them into a vial, or introducing them individually and separately in any order into a vial prior to sealing the vial. Suitably potassium clavulanate may be pre-mixed with sodium amoxycillin and then mixed with the desiccant material, and this mixture may then be introduced into a vial prior to
15 sealing the vial.

The method of protecting a moisture sensitive pharmaceutically active material contained in sealed containers from degradation by moisture provided by this invention may also be of use in the storage and transportation of such materials, for example by including such a desiccant in bulk pharmaceutically active material,
20 or a mixture comprising it, in a storage and/or transport container. Such a mixture may be a formulation suitable for administration by injection, or a component of such a formulation.

The invention will now be described by way of non-limiting example only.

25 1. Preparation of Desiccant Materials.

Desiccant materials were prepared by the following procedure:

	Desiccant Material	Initial Water %	Drying Treatment	Post-Drying Water %
30	CaCl ₂	22.03	Vacuum* 6h, 120°C	3.3
	MgCl ₂	52.5	Vacuum* 6h, 120°C	33.8
	sd-Lactose	5.1	Vacuum* 6h, 120°C	1.9
	NaCl	0.1	No Treatment	

35 (note: * vacuum = ca. 0-25 mbar; sd = "spray dried")

2. Desiccant : Formulation Blends Tested.

2200 mg of a 10 : 1 crystalline sodium amoxycillin (i.e. as described in EP

0131147) : potassium clavulanate blend (ratio expressed as weights of free acids equivalent) blended with:

- 5 A- sd-Lactose 500mg
 B- Sodium chloride 200mg
 C- Calcium chloride 50mg
 D- Magnesium chloride 50mg (equivalent to ca. 35 mg anhydrous MgCl₂)

- 10 These blends were sealed in vials with substantially airtight commercially available stoppers and were subjected to stability testing for 1 month at 37°C and 50°C. Reference standards for comparison were: R1 = commercially available spray-dried sodium amoxicillin : potassium clavulanate; R2 = crystalline sodium amoxicillin : potassium clavulanate. Both R1 and R2 were sealed in vials and
 15 stored under the conditions referred to above.

3. Results.

- 20 Content of the active constituents (clav. = clavulanic acid, amox. = amoxicillin) of the formulation is expressed as % of the initial value of the HPLC assay.

	1 month 37°C		1 month 50°C	
	Clav. %	Amox. %	Clav. %	Amox. %
R1	101.9	96.3	93.01	90.09
R2	96.36	99.32	90.91	99.53
25 A	98.65	100.48	93.70	99.06
B	96.15	99.87	92.57	98.03
C	98.27	99.09		
D	101.02	100.63	99.49	100.09

- 30 Colour variation at 1 month 50°C: R1 > R2/B > A/C/D

These results indicate the stability improvement against degradation by moisture of potassium clavulanate and sodium amoxicillin by the listed desiccants.

Claims:

1. A pharmaceutical formulation comprising a moisture sensitive pharmaceutically active material and a desiccant material, the desiccant being both water soluble and pharmaceutically acceptable by parenteral administration.
2. A pharmaceutical formulation according to claim 1 characterised in that the moisture sensitive pharmaceutically active material is one which is suitable for parenteral administration.
3. A pharmaceutical formulation according to claim 2 characterised in that the moisture sensitive pharmaceutically active material is a pharmaceutically acceptable derivative of clavulanic acid.
4. A pharmaceutical formulation according to claim 3 characterised in that the derivative of clavulanic acid is potassium clavulanate co-formulated with an injectable antibiotic.
5. A pharmaceutical formulation according to claim 4 characterised in that the antibiotic is crystalline sodium amoxycillin.
6. A pharmaceutical formulation according to any one of claims 1 to 5 characterised in that the desiccant is a desiccating metal salt which is water soluble and pharmaceutically acceptable when administered by injection.
7. A pharmaceutical formulation according to claim 6 characterised in that the desiccant metal salt is a Group I or Group II metal chloride or a mixture thereof.
8. A pharmaceutical formulation according to claim 7 characterised in that the desiccating metal salt is a desiccating form of sodium chloride, calcium chloride or magnesium chloride or a mixture thereof.
9. A pharmaceutical formulation according to any one of claims 1 to 5 characterised in that the desiccant is a desiccating carbohydrate which is water soluble and pharmaceutically acceptable when administered by injection.
10. A pharmaceutical formulation according to claim 9 characterised in that the desiccating carbohydrate is selected from lactose, sorbitol, and glucose, in an at

least partly dehydrated state.

11. A pharmaceutical formulation according to claim 9 characterised in that the desiccating carbohydrate is spray-dried lactose.
- 5 12. A pharmaceutical formulation according to any one of claims 1 to 5 characterised in that the desiccant is a desiccating form of a polyvinylpyrrolidone ("PVP") polymer.
- 10 13. A pharmaceutical formulation according to claim 1 comprising crystalline sodium amoxycillin, potassium clavulanate and as a desiccant magnesium chloride, sodium chloride or spray-dried lactose.
14. A pharmaceutical formulation according to any one of claims 1 to 13 being
- 15 a formulation which on reconstitution with water yields a solution which is suitable for administration by injection and provided in a sealed vial.
15. A method of preparing a pharmaceutical formulation according to any one of claims 1 to 14, comprising the steps of admixing a moisture sensitive
- 20 pharmaceutically active material and a desiccant, the desiccant being both water soluble and pharmaceutically acceptable by injection or infusion, and optionally sealing the formulation into a vial,.
16. A pharmaceutical formulation according to any one of claims 1 to 14 for use
- 25 as an active therapeutic substance.
17. The use of such a formulation as claimed in any one of claims 1 to 13 in the preparation of a medicament.
- 30 18. A method for protecting a moisture sensitive pharmaceutically active material from degradation by moisture by the use of a desiccant material which is both water soluble and pharmaceutically acceptable by parenteral administration.
- 35 19. A method of treatment of a human patient which includes the step of the parenteral administration to a patient in need of such treatment of a formulation as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/02127

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/02 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 008 905 (BEECHAM GROUP LIMITED) 19 March 1980	1-5, 12, 14-19
Y	see claims 1,5-7 see page 8; example 6 ---	13
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 151 (C-584) 12 April 1989 & JP,A,63 307 824 (TEISAN SEIYAKU) 15 December 1988	1,2,6-8, 14-19
Y	see abstract ---	13
X	DATABASE WPI Section Ch, Week 8846, Derwent Publications Ltd., London, GB; Class B07, AN 88-325998 & JP,A,63 239 237 (TEISAN SEIYAKU) 5 October 1988	1,2,6-8, 14-19
Y	see abstract -----	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * "&" document member of the same patent family

Date of the actual completion of the international search

29 September 1995

Date of mailing of the international search report

- 6. 10. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/ 02127

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 19 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Trial Application No

PCT/EP 95/02127

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0008905	19-03-80	NONE	